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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/993,604
Filing Date: November 14, 2001
Appellant(s): ASHKENAZI ET AL.

Panpan Gao
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 3/18/08 appealing from the Office action mailed 9/18/08.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

U.S. Serial Number 09/997,542, filed 11/15/01, drawn to antibodies to PRO1281. The instant application is drawn to PRO1281 itself. The '542 application is also being appealed and an Examiner's Answer will also be submitted to the Board at approximately the same time.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

1. Declaration of Audrey Goddard, Ph.D. under 35 C.F.R. §1.132

2. Declaration of Avi Ashkenazi, Ph.D. under 35 C.F.R. §1.132

3. Orntoft, T.F., *et al.* Molecular & Cellular Proteomics - 1:37-45 (2002).

4. Hyman, E., *et al., Cancer Research* 62:6240-6245 (2002).

5. Pollack, J.R., *et al. Proc. Natl. Acad. Sci. USA* 99:12963-12968 (2002).

6. Hanna *et al.,* Pathology Associates Medical Laboratories (1999).

7. Pennica, et al. *Proc. Natl. Acad. Sci. USA Vol. 95, pp. 14717-14722, December 1998*

8. Konopka *et al., Proc. Natl. Acad. Sci. USA* 83: 4049-52, (1986).

9. Sen *et al.,* Current Opinion in Oncology, 12: 82-88, (2000). (cited June 2, 2003)

10. Godbout, R., *et al.,* J. Biol. Chem. - 273(33):21161-8 (1998).

11. Li *et al.,* 2006, Oncogene 25: 2628-2635.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 101

Claims 119-126 and 129-131 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a specific, substantial and credible asserted utility or a well-established utility. These claims are directed to polypeptides having various sequence homology to SEQ ID NO:326. However, the invention encompassed by these claims has no apparent or disclosed patentable utility. This rejection is consistent with the current utility guidelines, published 1/5/01, 66 FR 1092. The instant application has provided a description of an isolated protein. However, the instant application does not disclose a specific and substantial biological role of this protein or its significance.

However, it is clear from the instant specification that the claimed protein is what is termed an "orphan receptor" in the art. The instant application does not disclose the biological role of the claimed protein or its significance. Appellants disclose in the specification that the receptor is a secreted protein. However, this fact, alone, is insufficient to confer utility to the protein of the present invention. Therefore, the instant claims are drawn to a polynucleotide encoding a protein which has a yet undetermined function or biological significance. There is no actual and specific significance which can be attributed to said protein identified in the specification. For this reason, the instant invention is incomplete. In the absence of a knowledge of the natural ligands or biological significance of this protein, there is no immediately obvious patentable use for it. To employ a protein of the instant invention in the identification of substances which bind to and/or mediate activity of the said receptor is clearly to use it as the object of further research which has been determined by the courts to be a non-patentable utility. Since the instant specification does not disclose a "real-world" use for said protein then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. 101 as being useful.

Furthermore, since the protein of the invention is not supported by a specific and substantial asserted utility or a well-established utility, the chimeric proteins also lack utility.

Claim Rejections - 35 USC § 112, first paragraph - enablement

A. Claims 119-126 and 129-131 are rejected under 35 U.S.C. 112, first paragraph, as failing to adequately teach how to use the instant invention. Specifically, since the claimed invention is not supported by a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

B. Furthermore, even if the claims possessed utility under 35 USC 101, claims 119-123 and 129-131 would still be rejected under 35 USC 112, first paragraph, because the specification, while then being enabling for SEQ ID NO:325 and 326, does not reasonably provide enablement for polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity to SEQ ID NO:326, to the protein encoded by ATCC No. 203129, for the extracellular domain thereof, or for fusion proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. There is no functional limitation in the claims. The claims encompass an unreasonable number of inoperative polypeptides, or polynucleotides which encode these polypeptides, which the skilled artisan would not know how to use.

There are no working examples of polynucleotides or polypeptides less than 100% identical to SEQ ID NO:325 or 326, or the mature form thereof (i.e. lacking its signal peptide). The skilled artisan would not know how to use non-identical polypeptides on the basis of teachings in the prior art or specification unless they possessed a specific function disclosed in the instant specification, in which there is none. While the specification generally describes homologous proteins, Appellants still have not taught to which family of proteins the protein of the present invention belongs. The specification does not provide guidance for using polynucleotides encoding polypeptides related to (*i.e.,* 80%-99% identity) but not identical to SEQ ID NO:325 or 326 which do not have any specific, known function. The claims are broad because they do not require the claimed polypeptide to be identical to the disclosed sequence and because the claims have no functional limitation.

For these reasons, which include the complexity and unpredictability of the nature of the invention and art in terms of the diversity of proteases and lack of knowledge about function(s) of encompassed polypeptides structurally related to SEQ ID NO:325, the lack of direction or guidance for using polypeptides that are not identical to SEQ ID NO:326, and the breadth of the claims for structure without function, it would require undue experimentation to use the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 112, first paragraph – written description

Claims 119-123 and 129-131 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity with SEQ ID NO:326, and fusion proteins thereof. The claims do not require that the polypeptide of the present invention possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO:326, or encoded by SEQ ID NO:325, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

Claims 119-126 and 129-131 are rejected under 35 U.S.C. 102(b) as being anticipated by Baker et al. (WO 99/63088). The claims recite an isolated polypeptide at least 80% identical to SEQ ID NO:326 as well as polynucleotides encoding this protein, extracellular domains and chimeric polypeptides. Baker et al. teach a protein which is 100% identical to SEQ ID NO:326 of the present invention (Sequence Comparison). This protein would encompass all of the claimed variants of that of the present invention. Baker also teach chimeric peptides (page 350, line 15).

(10) Response to Argument

Claim Rejections - 35 USC § 101

Appellants begin by summarizing their arguments on pages 4-6 of the Brief and by reciting the legal standard for utility as well as numerous examples of case law on pages 7-10 of the Brief. The Examiner takes no issue with the definition of the legal standard, or the case law.

Appellants argue beginning on page 10 of the Brief that Example 170 of the specification discloses, using gene amplification data obtained from the well-known TaqMan PCR assay, that the gene encoding PRO1281 showed significant amplification, ranging from 2.099 fold to 2.219-fold in different colon primary tumors. Therefore, such a gene is useful as a marker for the diagnosis of colon cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. Appellants also argue that the Declaration by Dr. Goddard supports the assertion that the gene is a suitable marker for the diagnosis of cancer. The TaqMan assay is described on page 11 of the Brief.

These arguments have been considered, but are not deemed persuasive. First, it is pointed out that though Appellants state in the Brief that the results are "significant" there is no statistical analysis disclosed, nor is any formula disclosed showing how the data was analyzed in order to determine the significance of the amplification. Even if, as argued by Appellants with regard to the Goddard Declaration

(see pages 11-12 of the Brief), this 2-fold amplification was significant, again, this does not provide any significance to the encoded protein. However, it is noted that the Goddard Declaration states that:

> It is further my considered scientific opinion that an at least 2-fold increase in gene copy number in a tumor tissue sample relative to a normal i.e. non-tumor) sample is significant and useful in that the detected increase in gene copy number…

Therefore, it can be seen that this "significance" is, respectfully, based on opinion, not fact. In assessing the weight to be given expert testimony, the Examiner may properly consider, among other things, 1) the nature of the fact sought to be established, 2) the strength of any opposing evidence, 3) the interest of the expert in the outcome of the case, and 4) the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993).

Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Goddard is employed by the assignee and is an inventor in this application. Furthermore, The Declaration of Dr. Goddard does not teach the level of reproducibility or the level of reliability of the results. Furthermore, the declaration addresses whether the ΔCt values are significant, and not whether or not gene amplification correlates with polypeptide levels. Also, the controls used in the instant invention were not matched, non-tumor lung samples, but rather was a pooled DNA sample from blood of healthy subjects. The art uses matched tissue samples (see Pennica et al.).

Regarding the strength of opposing evidence, at pages 539-554 of the specification, Example 170 discloses a gene amplification assay in which genomic DNA encoding PRO1281 had a ΔCt value of 1.07 and 1.15 for the two colon tumor samples when compared to a pooled control of blood DNA from several healthy volunteers. While Appellants argue that the issue as to whether or not the fact that PRO1281 is amplified in most colon tumors is irrelevant, the fact that only two colon tumors (CT2 and CT12) were tested makes it difficult to conclude that it would be more likely than not that other colon tumors could be identified in this manner. In other words, the sample size of "2" is small.

It appears that Appellants' arguments on page 12 of the Brief regarding PRO1281 polynucleotide expression in 2 out of 14 colon tumors (as well as the Examiner's initial argument raising this issue) is incorrect as, from Table 9C on page 554 of the specification, it can be seen that only two colon tumors were tested.

On page 13 of the Brief, Appellants argue that detection of gene amplification can be used for cancer diagnosis regardless of whether the increase in gene copy number results from aneuploidy. Appellants refer to the declaration of Dr. Ashkenazi in support of this position. This has been fully considered but is not found to be persuasive. As discussed above, Sen (2000, Curr. Opin. Oncol. 12:82-88) teaches that cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes. A slight amplification of a gene does not necessarily correlate with overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. Aneuploidy is a feature of damaged tissue, and is commonly found in lung and colon tissues, which are subject to environmental influences. Such does not invariably lead to cancer; rather, the development of cancer is rare, as evidenced for example by the fact that the general population is constantly suffering damage to lung cells via air pollution, whereas lung cancer remains relatively rare. The gene amplification assay in the instant specification does not provide a comparison between colon cancer and normal colon samples, and does not correct for aneuploidy. Thus it is not clear that PRO1281 is amplified in cancerous colon epithelium more than in damaged (non-cancerous) lung or colon epithelium. One skilled in the art would not conclude that PRO1281 is a diagnostic probe for lung cancer or a target for therapeutic drug development unless it is clear that PRO1281 is amplified

Even, arguendo, the Declaration by Ashkenazi and Sen support Appellants' position, the fact remains that Appellants are attempting to provide utility to the claimed protein based on information about the encoding DNA (gene). However, the fact that the gene may or may not have a utility does not necessarily confer a utility to the encoded protein. This issue has been discussed throughout prosecution of this application. The fact that Appellants used the well-known TaqMan PCR assay does not persuade the Examiner since this assay is focused on DNA and does not relate to, nor provide any utility for any protein encoded by that amplified DNA.

On pages 13-14 of the Brief, Appellants argue that “it is not a legal requirement that gene amplification 'necessarily' results in increased expression at the mRNA and polypeptide levels, or that the polypeptide levels can be 'accurately predicted.'” Appellants submit that “the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility." Based on this, Appellants argue that neither of the references cited by the Examiner (Pennica et al., Konopka et al.) supports a lack of utility and that "when the proper evidentiary standard is applied, a correlation must be acknowledged.”

The Examiner and Appellants are in basic agreement as to the teachings of Pennica (page 14 of the Brief). Appellants' conclusion is that, given Pennica and "the working hypothesis among those skilled in the art, that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level." This argument has been considered, but is not deemed persuasive. The instant rejection relies upon several references evidencing that it is more likely than not that gene amplification is a result of non-specific aneuploidy and is not associated with mRNA or polypeptide overexpression. See Pennica et al., Godbout et al., Li et al., and Sen. While these references, taken together, including the fact that, as Appellants argue, Pennica "has no teaching whatsoever about the correlation of gene amplification and protein expression in general" can be used to demonstrate that it cannot be guaranteed that polypeptide levels do, or do not correlate with DNA levels, the artisan can conclude that the art is at least contradictory as to whether it is more likely than not that a correlation exists.

Furthermore, on page 15 of the Brief, Appellants further argue that the Examiner's citing of Konopka was inappropriate since Konopka only teach the *abl* gene. This argument has been considered, but is not deemed persuasive. In fact, Konopka supports the Examiner's position that protein levels cannot be predicted from gene expression. This can be seen in Appellants' quotation from Konopka which states "protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph template." This, in view of Pennica, make a strong argument about predicting protein levels from DNA overexpression. Again, while Appellants argue that this specific example cannot be used to support a general conclusion it can be used, as discussed in the above paragraph, that the art is at least contradictory as to whether it is more likely than not that a correlation exists.

To summarize, based on the detailed consideration of the evidence of record (both supplied by Appellants and relied upon by the Examiner) it is clear that it is more likely than not that a small gene amplification in a very small percentage of cancer samples does not impute a patentable utility on the encoded polypeptide.

Regarding the Godbout reference, Appellants argue that this reference was never claimed that PRO1281 is in any way similar to the DDX1 gene of Godbout. The Examiner agrees. Appellants further state that, on the other hand, Godbout was submitted to show good correlation between protein levels based upon genomic DNA amplification. To this effect, the Examiner points out that Godbout also teach that "*It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell.*" There is no evidence or assertion of record that PRO1281

provides a selective growth advantage to a cell, and thus it cannot be presumed that the polypeptide is overexpressed because the genomic DNA, including the gene being studied, is amplified.

On pages 15-16 of the Brief, Appellants discuss Li et al., Hyman et al., and Pollack et al. and argue that, in Li, genes were considered to be amplified if they had a copy number ratio of at least 1.40 and that PRO1281 showed a copy number of at least 2.0. While Appellants argue that "Li do not conclusively disprove that a gene with a substantially higher level of gene amplification, such as PRO1281, would be expected to show a corresponding increase in transcript expression" the Examiner notes that the discussion of Li and Appellants' arguments focus on DNA amplification with no discussion of a correlation (or absence thereof) to protein expression. In fact, Li et al. (2006, Oncogene, Vol. 25, pages 2628-2635) state: "***In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels***, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but *lack biological relevance in terms of the development of lung adenocarcinoma*." Since more than half of the amplified genes were not overexpressed, Li et al. constitutes strong evidence that ***it is more likely than not that gene amplification does NOT correlate with increased protein levels***, absent evidence that the polypeptide has biological relevance in cancer. There is no such evidence for PRO1281. Therefore, there is ample evidence that only those genes which confer a selective advantage to a cell are overexpressed in cancer cells.

Furthermore, it is noted, in contrast to Appellants' statements regarding the different methodologies between Li and Hyman, that Hyman also found that less than half of the amplified genes were overexpressed at the mRNA level, even though they only investigated genes in genomic DNA regions that were amplified at least 2-fold (argued in more detail above), and thus Hyman et al. supports the examiner's position. Furthermore, Li et al. did not limit their studies to genes that were amplified at less than 2-fold. In fact, the supplemental information indicates that some of the samples were required to bind with a probe requiring at least 2-fold amplification:

> Genes with copy number ratio > 1.40 (representing the upper 5% of the CGH ratios across all experiments) were considered to be overrepresented. A genomic fragment that contained six or more adjacent probes showing a copy number ratio > 1.40, or a region with at least three adjacent probes with a copy number ratio > 1.40 **and no less than one probe with a ratio > 2.0**, were considered to be amplicons. (emphasis added, from 1st page of supplemental material)

At page 16 of the Brief, Appellants argue that it is "more likely than not" for amplified genes to have increased mRNA and protein levels. Appellant refers to Orntoft et al., Hyman et al., and Pollack et al. as evidencing that, in general, gene amplification increases mRNA expression. This has been fully considered but is not found to be persuasive. First, Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification. In fact, respectfully, none of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in colon cancer.

Furthermore, Orntoft et al. could only compare the levels of about 40 well-resolved and focused *abundant* proteins." (See abstract). It would appear that Appellants have provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded polypeptide.

Furthermore, Orntoft et al. appears to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and polypeptide levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding cDNA amplification of individual gene, which may or may not be in a chromosomal region, which that is highly amplified. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (see page 40).

Hyman et al. found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO1281 would be correlated with elevated levels of mRNA, much less polypeptide. Since Hyman et al. found that less than half of the amplified genes were overexpressed at the mRNA level, Hyman et al. supports the basis of the rejections that it is more likely than not that gene amplification *fails* to correlate with increased mRNA/polypeptide levels. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification. None of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in lung or colon cancer.

At page 18 of the Brief, Appellants urge that Pollack et al. profiled DNA copy number alteration across 6,691 mapped human genes in breast cancer samples, and compared such to mRNA levels determined by microarray analysis. Appellant quotes from Pollack et al.'s conclusion of a strong correlation between highly amplified genes and elevated mRNA expression. Though Appellants argue that the CGH methodologies used are not traditional, Pollack still restricted their investigation to genes that are located in relatively large chromosomal areas experiencing amplification. There is no evidence that the PRO1281 gene comes from such a chromosomal area. Furthermore, Pollack et al. limited their conclusion to the regions that were "highly amplified." Finally, it is interesting to note that Pollack et al. found correlations in their breast cancer samples, but referred to another investigative group that found very poor correlations in colon cancer samples. See bottom of right column of p. 12967 of Pollack et al. wherein they discuss Platzer et al. Also interesting is that Pollack et al. used a normal female leukocyte DNA control from a single donor rather than normal breast tissue (matched tissue control), whereas Platzer et al. compared colon cancer samples to normal colon epithelium.

On page 19 of the Brief, Appellants argue the Ashkenazi declaration. The Examiner argues that the declaration supports the rejections in admitting that amplified genes may not correlate with gene product overexpression. It is also important to note that the specification never suggests using such information for tumor categorization or to develop more suitable therapies. In fact, other than a general assertion that an antibody can be used therapeutically, no "suitable therapy" is suggested for cancers that may be represented by the samples assayed in the instant specification.

On page 20 of the Brief, Appellants addresss the Hanna and Mornin publication. Appellant reviews the disclosure of Hanna and Mornin, and argues that Hanna and Mornin support the Ashkenazi declaration. Appellant urges that the examiner has misread Hanna and Mornin, in that Hanna and Mornin clearly state that gene amplification and polypeptide expression generally correlate well. This has been fully considered but is not found to be persuasive. Hanna and Mornin provide an important example of a lack of correlation between gene amplification and mRNA/polypeptide overexpression, wherein diagnosis of breast cancer included testing both the amplification of the HER-2/neu gene as well as over-expression of the HER-2/neu gene product. Thus Hanna and Mornin provide evidence that the level of polypeptide expression *cannot* be presumed, but rather *must* be tested empirically to determine whether or not the polypeptide can be used as a diagnostic marker for a cancer. The specification does not provide data as to whether or not the polypeptide level of PRO1281 was tested in normal and cancerous tissue, and thus the skilled artisan *must* perform additional experiments, as directed by the art. Since the asserted utility for

the claimed antibodies is not in currently available form, and further experimentation is *required* to reasonably confirm the asserted real-world use, the asserted utility is not substantial.

With regard to Appellants' arguments on page 17 that use of microarrays provides a utility for the present invention (Affymetrix) is not persuasive since, first, microarrays involve the use of DNA, not proteins. Second, it is the microarray as a whole which has been useful to the industry, not the individual genes.

It is believed that all pertinent arguments have been addressed.

Claim Rejections - 35 USC § 112, first paragraph – enablement

A. Claims 119-126 and 129-131 remain rejected under 35 USC 112, first paragraph, for the reasons discussed above under 35 USC 101. Appellants have not argued this point. Therefore, the arguments are being considered identical to those argued above regarding 35 USC 101.

B. Appellants argue that the claims recite structural features, namely, 80-99% sequence identity to SEQ ID N0:326, which are common to the genus. The genus of claimed polypeptides is further defined by having a specific functional activity for the encoding nucleic acids, namely, that the encoding nucleic acid is amplified in colon tumors. The specification provides detailed guidance as to how to identify the recited variants of SEQ ID N0:326, including methods for determining percent identity between two amino acid sequences, as well as listings of exemplary and preferred sequence substitutions, as well as detailed protocols for determining whether a gene encoding a variant PRO1281 protein is amplified in colon tumor. Thus one of skill in the art could easily identify whether a variant PRO1281 sequence falls within the parameters of the claimed invention.

These arguments have been considered, but are not deemed persuasive.

Even if one of skilled in the art was able to generate polypeptides that are 80%- 99% identical to SEQ ID NO: 326, it will require undue experimentation to assign the functional limitations to these polypeptides. Although, Appellants have amended the claims to assert that the said polypeptide is overexpressed in colon tumor tissue compared to normal colon tissue there is no way of knowing which, if any, variants or fragments would have the same property of overexpression in the specific tissue. There is no nexus between the degree of homology and regulation of gene expression. Until one identifies a particular variant that demonstrates an altered expression, one of skilled in the art would not know the

expression profile of the variant. Modifications to the protein, e.g., by substitutions or deletions, would often result in deleterious effects to overall activity and effectiveness of the protein.

Furthermore, the disclosure fails to enable such a myriad of the claimed polypeptide molecules that not only vary substantially in length, but also in amino acid composition and to provide any guidance to one skilled in the art on how to make and use the claimed genus of polypeptide molecules. In summary, the lack of guidance presented in the specification regarding which variants of polypeptides of SED ID NO:326 would retain the desired activity, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity, the absence of working examples directed to variants and the breath of claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, first paragraph – written description

Appellants note that the claims recite structural features, namely, 80-99% sequence identity to SEQ ID NO:326, which are common to the genus. The genus of claimed polypeptides is further defined by having a specific functional activity for the encoding nucleic acids, namely, that the encoding nucleic acid is amplified in colon tumors. The specification provides detailed guidance as to how to identify the recited variants of SEQ ID NO:326, including methods for determining percent identity between two amino acid sequences, as well as listings of exemplary and preferred sequence substitutions, as well as detailed protocols for determining whether a gene encoding a variant PRO1281 protein is amplified in colon tumor. Thus one of skill in the art could easily identify whether a variant PRO1281 sequence falls within the parameters of the claimed invention. Accordingly, a description of the claimed genus has been achieved by the recitation of both structural and functional characteristics, namely, amplification in colon tumors.

These arguments have been considered, but are not deemed persuasive for the reasons provided above under 35 USC 112, first paragraph, lack of enablement. Applicants' arguments are nearly identical for both 35 USC 112, first paragraph, issues regarding percent identity.

Furthermore, the specification provides a written description of only one protein in the genus (SEQ ID NO:326). No other species are described, or structurally contemplated, within the instant specification. Therefore, one skilled in the art cannot reasonably visualize or predict critical amino acid residues which would structurally characterize the genus of proteins claimed; thereby not meeting the

written description requirement under 35 USC 112, first paragraph. Thought the specification may describe methods to identify polypeptides at least 80% identical to SEQ ID NO:326 and though the artisan can physically identify polypeptides which are 80% identical to SEQ ID NO:326 and which are overexpressed in colon tumors, Appellants still have not provided adequate written description of a sufficient number of polypeptides in the claimed genus.

Even a very skilled artisan could not envision the detailed chemical structure of all or a significant number of encompassed SEQ ID NO:326 polypeptides. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of making. The claimed product itself is required. Recitation of the phrase "wherein the polypeptide is amplified in colon tumors" is not adequate to describe polypeptides having 80-99% homology to SEQ ID NO:326, since there was no reduction to practice to support the claims. Specifically, there is no way of knowing which, if any variants would have the same property of over-expression in colon tissues. There is no nexus between the degree of homology and regulation of gene expression. Until one identifies a particular variant which is, or is not, over-expressed, one of skilled in the art would not know the expression profile of the variant. The mere sequence alone will not allow one of skilled in the art to predict expression. Appellants made no variant polypeptides, and as recited in the current Written Description Guidelines, Appellants must have invented the subject matter that is claimed and must be in "possession" of the claimed genus (Federal Register, 2001, Vol. 66, No. 4, pages 1099-1111, esp. page 1104, 3rd column).

It is believed that all pertinent arguments have been addressed.

Claim Rejections - 35 USC § 102

Appellants submit that U.S. provisional application 60/141,037 has utility based on the gene amplification assay and further that they have made a proper priority claim to U.S. provisional application 60/141037, filed June 23, 1999. Therefore, Baker et al. is not prior art. However, for the reasons presented above under 35 USC 101, Appellants' arguments are not deemed persuasive.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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